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Comments:

Resending per your phone call

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July 15, 2010

Dr. Taranisia MacCannell
Division of Healthcare Quality Promotion
The Centers for Disease Control and Prevention
1600 Clifton Boulevard
Atlanta, GA 30333

SUBJECT: RESPONSE TO HICPAC NOROVIRUS GUIDELINE

Dear Dr. MacCannell:

We applaud your recent efforts to create the Draft Guidelines for the Prevention and Control of Norovirus Gastroenteritis Outbreaks in Healthcare Settings. As a leading company in hand hygiene for infection control and prevention, and the creator of PURELL® Instant Hand Sanitizer, the leading hand sanitizer in North America, GOJO understands and appreciates the value of collaborative, scientific evidence-based guidelines to improve patient safety and outcomes.

Our review of the document confirms that you have incorporated a number of evidenced based best practices and principles into the recommendations and standards. However, we have one editorial recommendation relative to the recommendations for use of alcohol based hand sanitizers during the care of patients with norovirus, and several comments regarding the science around hand sanitizers and norovirus.

FDA Approval

In the section of Recommendation Q3, specifically 3.C.1.b.1, the statement "consider FDA-approved alcohol-based hand sanitizers..." leaves the question of what is meant by FDA approval. Our experience suggests this wording will create confusion in the market since the FDA does not formally approve the vast majority of hand sanitizers individually. We request that this wording be changed to clarify that products that are "compliant (monograph or NDA)" would meet the definition of FDA approved in this context. The concern centers on potentially misinterpreted language: the term "FDA Approved" products could lead some to only include those that received market approval from FDA through the New Drug Application (NDA) process and exclude those that are marketed in compliance with the OTC drug review process under the monograph system. The FDA clearly states that FDA Approval via a New Drug Approval (NDA) and FDA Compliance with a Monograph require a product to achieve the same level of safety and effectiveness. (i.e., "neither mechanism establishes higher standards for safety or effectiveness than the other").[1]

Page and Item Number	Current Language	Proposed Language	Rationale
Page 12, Item 3.C.1.b.1	3.C.1.b.1 During outbreaks, use of soap and water is the preferred method of hand hygiene. Consider FDA-approved alcohol-based hand sanitizers as a supplemental method of hand hygiene during outbreaks of norovirus gastroenteritis when hands are not visibly soiled and have not been in contact with diarrheal patients, contaminated surfaces, or blood or other body fluids. **(Category II)** (Key Question 3C)	3.C.1.b.1 During outbreaks, use of soap and water is the preferred method of hand hygiene. Consider FDA-~~approved~~ **compliant (monograph or NDA)** alcohol-based hand sanitizers as a supplemental method of hand hygiene during outbreaks of norovirus gastroenteritis when hands are not visibly soiled and have not been in contact with diarrheal patients, contaminated surfaces, or blood or other body fluids. **(Category II)** (Key Question 3C)	Clarify that products marketed in compliance with the OTC drug review or healthcare antiseptic monograph are acceptable in addition to products marketed under an NDA.

SCIENCE AROUND HAND SANITIZERS AND NOROVIRUS

Section 3.C.1.b.2 states that "Further research is required to directly evaluate the efficacy of alcohol-based hand sanitizers against human strains of norovirus, or against a surrogate virus with properties convergent with human strains of norovirus". We agree with this statement and want to share relevant recent research and our scientific perspective to further support the Hand Hygiene recommendations. Comments below are based primarily on literature not included or published after the February 2008 literature review cutoff date:

1) **Research to evaluate the activity of hand sanitizers has been hindered by the lack of an *in vitro* tissue culture system for human norovirus.** In 2007, Straub *et al.* published a cell culture infectivity assay for human norovirus.[2] While this method initially showed promise, to our understanding the work has not been repeatable and consequently cannot be used to evaluate antimicrobial products. In the absence of an *in vitro* tissue culture system, researchers have focused on animal surrogate viruses and results have been extrapolated to make inferences regarding the behavior of human norovirus. We support the recommendation for research to establish reliable assays for human norovirus.

2) **The two currently accepted NoV surrogates have distinct antimicrobial susceptibility profiles and may not accurately predict activity of antimicrobial products against human norovirus.** As stated in the Draft Guidelines, studies using feline calicivirus (FCV) as a surrogate reveal relatively low $\log_{10}$ reductions, even at

ethanol concentrations of 95%. This is not surprising as Gehrke *et al.* (ref. 196) found that inactivation of FCV was maximal at concentrations near 70% and decreased at higher concentrations.[3] In contrast to FCV, recent studies have found murine norovirus (MNV) to be relatively sensitive to ethanol; with concentrations as low as 60% ethanol achieving greater than a 4 $\log_{10}$ reduction in 30 seconds.[4,5] In addition, Cannon *et al.* (ref. 20) demonstrated that FCV is unstable at low pH calling into question its appropriateness as a surrogate for gastrointestinal viruses.[6] Without a reliable human norovirus infectivity assay, it remains unknown which surrogate more accurately predicts the susceptibility of human norovirus to ethanol. The current thinking in the scientific community is that MNV is a more appropriate surrogate based on multiple factors. We agree with this position but feel that data on human norovirus is required before stronger conclusions and recommendations can be made.

3) **Molecular detection methods have been recently developed to quantify human norovirus.** Several recent papers have used quantitative Real-Time PCR (RT-qPCR) to detect human norovirus RNA as a surrogate for infectivity.[7-10] These studies have opened the door to future studies to more effectively evaluate the activity of hand hygiene interventions. Further research is needed to determine the level of correlation between RT-qPCR based methods and norovirus infectivity.

4) **Alcohol level is not the only factor influencing the antiviral activity of hand sanitizers.** In addition to ref. 189 which demonstrated that a mixture of ethanol, diols and phosphoric acid exhibits improved inactivation of non-enveloped viruses, a recent study by Macinga *et al.* demonstrated that a mixture of ethanol, a cationic polymer and citric acid exhibited improved inactivation of multiple non-enveloped viruses including FCV and MNV.[11,12] We are continuing our efforts in this area, understanding the critical need for highly effective hand hygiene products for human norovirus. Further research is needed to determine the relationship between laboratory studies and clinical infection control benefit.

We appreciate your consideration. We would also like to commend the Division of Healthcare Quality Promotion (DHQP) and the Division of Viral Disease (DVD) for their pilot project, "The Norovirus Guideline Toolkit". GOJO is committed to advancement of hand hygiene and infection control and welcomes the opportunity to participate. If you have any thoughts on how we might add value on this study or future projects, please contact us directly.

Respectfully submitted,

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References:

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